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**A Prospective Trial of Minimal Intensity Conditioning with Fludarabine and Anti-CD52 Antibody Alone in Dyskeratosis Congenita**

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**Background:** Dyskeratosis congenita (DC) is an inherited bone marrow failure (BMF) syndrome classically presenting with a clinical triad of skin pigment abnormalities, nail dystrophy, and oral leukoplakia. Progressive BMF occurs in approximately 80% of patients by 30 years of age and is the primary cause of death, followed by pulmonary failure and malignancies. HCT for DC is limited by a high incidence of treatment-related mortality, due to the exacerbation of underlying multi-organ disease by alkylating agents and radiation in the conditioning regimen. DC is caused by lesions in telomere biology genes, which compromise cellular replicative capacity. Because of this intrinsic cellular defect, we hypothesize that DC patients will show acceptable rates of engraftment with a minimally cytotoxic conditioning regimen that excludes alkylating agents and radiation. Vuong *et al.* (*Acta Haematologica*, 2010) have previously reported successful engraftment in a single DC patient using fludarabine and antithymocyte globulin conditioning. Based on this rationale and experience, we initiated a prospective HCT trial with immunosuppression-only conditioning, which would be predicted to improve outcomes and reduce secondary malignancies in DC patients.

**Methods:** Patients up to age 30 years old with a well-matched bone marrow donor are conditioned with anti-CD52 and fludarabine, and receive cyclosporine A and mycophenolate mofetil as graft versus host disease (GVHD) prophylaxis. Primary outcome measures include neutrophil engraftment at day +30 and survival at day +100, and secondary outcome measures include rates of graft failure, infections, GVHD, secondary malignancies, and acute and long-term toxicities.

**Results:** 3 patients with DC underwent unrelated donor HCT with one-year follow-up. 18 month-old identical twins with *TINF2* mutations and transfusion-dependent BMF received HCT from a fully HLA-matched donor, and were platelet-independent and neutrophil engrafted by day +28. Myeloid chimerism was consistently fully donor. Lymphoid chimerism was <10% donor on day +100, and increased to 88-95% donor by one year post-transplant. The third patient was an 18 year-old female with DC due to *CTC1* mutations and transfusion-dependent BMF, who underwent single allele (HLA B) mismatched HCT. She was platelet-independent and neutrophil-engrafted by day +21. Myeloid and lymphoid chimerism were fully donor in the post-transplant period. Currently one year post-HCT, all three patients are transfusion-independent and off immunosuppression without significant toxicities.

**Conclusions:** Early data suggest the feasibility of an immunosuppression-only conditioning regimen for allogeneic HCT in patients with DC. Ongoing studies will determine the general applicability of this regimen in a disease as heterogeneous as DC, and longer-term follow-up will reveal the impact on late effects.

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**High-Dose Chemotherapy with Busulfex and Melphalan As Conditioning Regimen Followed By Autologous STEM CELL Rescue for Pediatric Patients with High-Risk Neuroblastoma**

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**Introduction:** High-dose chemotherapy with stem cell rescue (auto-transplant) became a well established consolidation procedure for high-risk neuroblastoma patients. We summarize our cumulative experience using busulfex and melphalan rather than carboplatin/etoposide/melphalan as preparative regimen for transplanting these pediatric patients.

**Patients & Methods:** Six pediatric patients aged 4-10 year old (median 5.75 year old), 3 males and 3 females underwent auto-transplant. All received busulfex 0.95-1.1mg/kg/dose, 16 doses on days -7 to -3 and melphalan 140mg/m<sup>2</sup>, one dose on day -1. Busulfex levels were measured and appeared to range between 981-1222mM per minute (median: 1136mM per minute), with no correction needed (normal level range of 850-1400mM per minute). Cell reconstitution included total nuclear cell (TNC) dose of 5.01-23.7x10<sup>8</sup>/kg (median 15.2x10<sup>8</sup>/kg) cells, and CD34+ cell content of 4.15-9.58x10<sup>6</sup>/kg (median 6.26x10<sup>6</sup>/kg) cells.

**Results:** Conditioning was well tolerated. No patient developed veno-occlusive-disease (VOD) of the liver. Trilineage engraftment was documented in all patients and none exhibited graft failure. Time to recovery of absolute neutrophil count >0.5x10<sup>9</sup>/L was 9 - 11 (median 9) days. The time to platelet recovery >or=20 and >or=50x10<sup>9</sup>/L ranged from 11 to 12 (median 12) days, and from 12 to 32 (median 22) days, respectively. One patient did not achieve platelets count above 20x10<sup>9</sup>/L and another one did not achieve platelets count above 50x10<sup>9</sup>/L, before their discharge. Hospitalization period ranged between 23-29 days (median: 26 days). Moderate to severe mucositis was the major adverse event post transplant, causing all patients to be supported by total parental nutrition (TPN) for 7-12 days (median: 11 days). Three patients suffered from culture-negative febrile neutropenia and received antibiotics until neutrophil engraftment. Transplant-related mortality did not occur in any of the patients.

**Conclusions:** Busulfex and melphalan -based preparative protocols are well tolerated, facilitate rapid engraftment with minimal toxicity, and may be considered for pediatric patients with high-risk neuroblastoma in need for auto-transplant. Larger cohort of patients is needed to further confirm our results.

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**Prevalence and Impact of Poverty in Pediatric Allogeneic Hematopoietic Stem Cell Transplant**

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**Background:** Despite emerging evidence of substantial financial distress in families of children with cancer, little is known about the impact of economic hardship on pediatric

hematopoietic stem cell transplant (HSCT) outcomes. Poverty is known to be correlated with negative health outcomes in pediatric primary care and subspecialties; it is not known how poverty impacts HSCT outcomes.

**Objective:** To describe the baseline prevalence of poverty and material hardship in the pediatric HSCT population at a major referral center. To describe transplant-related work disruptions and income losses stratified by federal poverty level (FPL) in this patient population, and explore the relationship between family poverty and clinical outcomes.

**Methods:** Single institution, cross-sectional survey. Participants included 45 English-speaking, pediatric allogeneic HSCT families whose children had undergone HSCT in the prior twelve months and were alive at time of survey administration. Eighty-seven percent of families approached consented to study participation. This study was approved by the Dana-Farber Cancer Institute Institutional Review Board.

**Results:** Poverty prior to transplant was prevalent with 18 (40%) families reporting baseline incomes at or below 200% FPL (\$44,000 for a family of four). Parental work disruptions due to HSCT were common across all income levels with 39 (87%) families reporting some disruption, and consequent income losses were substantial for all families. Families at or below 200% FPL were disproportionately impacted with 7 (39%) of the poorest families reporting transplant-associated annual income losses of >40% as compared to 2 (18%) of the wealthiest families ( $p=0.006$ ). Material hardship during the post-transplant period was widespread, with 17 (38%) families reporting either food, housing, or energy insecurity. Baseline family poverty level was not associated with length of transplant admission, unplanned re-admissions, or ICU stay in the 6-month post-transplant period in univariate analysis. Poorer children, however, were more likely to experience Graft Versus Host Disease (GVHD) of any grade in the 6 month post-transplant period with eleven (61%) of those at or below 200% FPL experiencing GVHD as compared with 2 (18%) of the wealthiest ( $p=0.01$ ).

**Conclusion:** Baseline poverty is widely prevalent in the pediatric HSCT population, and poverty may be associated with the development of GVHD. Material hardship during the post-transplant period—including food, housing, or energy insecurity—is widespread. Further studies aimed at understanding how these social determinants of health contribute to HSCT outcomes may provide targetable factors to decrease transplant-associated morbidity and mortality.

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### Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Non Malignant Hematologic Disorders (NMHD), Using a Chemotherapy-Only Cytoablative Regimen and T-Cell Depleted Grafts from Alternative Donors

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Non-malignant hematologic disorders of childhood comprise a number of various disorders including acquired severe aplastic anemia (SAA), and inherited marrow failure syndromes. Patients with such diseases who do not have matched related donors fare poorly with allogeneic HSCT from alternative donors and are at high risk for developing chronic GVHD. We report 14 patients aged 0.7–18 years of age (median 5.3 years) who received T-cell depleted HSCT from

alternative donors between April 2005 and May 2013. Diseases included acquired SAA including PNH (N=6), severe chronic neutropenia (SCN)(N=2), congenital amegakaryocytic thrombocytopenia (N=2), Shwachman Diamond syndrome (N=1), autoimmune hemolytic anemia (N=1), chronic granulomatous disease (N=1) and hemophagocytic lymphohistiocytosis (N=1). Two patients with SAA had constitutional abnormalities and were therefore thought to have possibly genetic diseases despite negative testing for defined disorders. Ten patients had long standing symptomatic disease for > 1 year prior to transplant. Patients with Fanconi anemia and dyskeratosis congenita were treated with reduced intensity regimens and were not included. Patients received one of 3 myeloablative regimens: Busulfan Melphalan and Fludarabine (N=2), Cyclophosphamide Thio Flu (N=3) or Mel, Thio Flu (N=9). Patients received rabbit ATG pre-transplant and filgrastim post transplant to promote engraftment. Donors were unrelated HLA-matched donors (N=5), unrelated HLA-mismatched donors (N=6) or related HLA-mismatched donors (N=2), and related phenotypic matched donor (N=1). Grafts included soybean agglutinin negative, E-rosette negative bone marrow grafts (N=5), Isolex CD34+ E-rosette- peripheral blood stem cell grafts (N = 4), or CliniMACS CD34+ PBSC grafts (N=5).

All 13 evaluable patients engrafted. Neutrophil engraftment occurred on day +12 and platelet engraftment to 20,000 on day +20 post transplant. Four patients died from multi-organ failure and/or infection (three of whom had a duration of their disease of 2–7 years). One patient with SAA fully engrafted with donor cells developed a pancytopenia post transplant with secondary MDS in donor cells; this patient is alive. Excluding one patient who is too early post transplant and with a median follow-up of 2 years, 8 of 13 patients are alive (OS 61%). None of these patients has evidence of GVHD. These results should encourage proceeding to transplant with chemotherapy-only cytoablative regimens and T-cell depleted stem cell transplants from alternative donors for patients with non malignant hematologic disorders earlier in the course of their disease.

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### Lymphopenia in Patients with Hemophagocytic Lymphohistiocytosis: Are B Cells Suppressed in These Patients?

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**Background:** Hemophagocytic Lymphohistiocytosis (HLH) is an immune regulatory disorder requiring allogeneic hematopoietic stem cell transfusion (HSCT) for long-term survival. More importantly, it is imperative to initiate treatment early as delays in treatment can be associated with significant mortality. Unfortunately, there can be significant overlap of the HLH diagnostic criteria with other non-HLH conditions, thereby considerably delaying diagnosis and therapy for HLH. Hence, surrogate markers are needed to aid in the diagnosis and prevent delays in initiating therapy in this life threatening disorder. Hypogammaglobulinemia has been a less commonly reported feature of HLH. It has been reported in SAP deficient patients +/- HLH. More recently, it has been reported in a few patients with XIAP deficiency and STXBP2 mutations in association with colitis. We have observed B-cell lymphopenia as well as hypogammaglobulinemia in patients with HLH at our institution. However, the